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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1609	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,778	HANING ET AL.	
	Examiner	Art Unit	
	Walter E. Webb	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☒ Claim(s) *3 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/03/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-10 are pending and rejected.

Claims 3 and 9 are objected to.

Claim Objections

Claims 3 and 9 are objected to because of the following informalities: these claims both repeat diseases unnecessarily. For example, improving perception, concentration performance, learning performance, and vascular dementia are mentioned more than once in the same claim. Appropriate correction is required.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

`Arrangement of the Specification`

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Applicant has not provided section headings for the different aspects of the specification such as Title of the Invention, Background of the Invention, Brief Summary of the Invention, and Detailed Description of the Invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of most diseases of claims 1-3 and 7-9, with exception of multiple sclerosis (MS) and amyolateral sclerosis (ALS) (claim 3), does not reasonably provide enablement for treating and certainly not the prevention of MS or ALS, or the prevention/cure for any of the other diseases of claims 1-3 and 7-9. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision In re Wands, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;

2) the breadth of the claims;

3) the predictability or unpredictability of the art;

4) the amount of direction or guidance presented;

5) the presence or absence of working examples;

6) the quantity of experimentation necessary;

7) the state of the prior art; and,

8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

Factors 1 and 2: Applicant's invention is drawn to a method for treating and or prophylaxis (prevention) of diseases in which an improvement in and/ or a cure of a syndrome can be achieved by improving the microcirculation of a tissue, which contains a cGMP-metabolizing phosphodiesterase by administering a cGMP-stimulating compound (claim 1). The diseases of claims 2, 3 and 7-9 are: coronary heart disease, cardiac insufficiency, pulmonary hypertension, bladder diseases, prostate hyperplasia,

nitrate-induced tolerance or diseases of the eye, central retinal or posterior cilliary arterial occlusion, central retinal venous occlusion, optical neuropathy, and also macular degeneration, and diabetes, and disturbances in the peristalsis of the stomach and esophagus, of female infertility, premature labor, preeclampsia, alopecia, psoriasis, the renal syndrome, cystic fibrosis, improving perception, concentration performance and learning performance and/or memory performance, for improving perception, concentration performance, learning performance and/or memory performance following cognitive disturbances, age-associated learning and memory disturbances, age-associated memory loss, vascular dementia, craniocerebral trauma, stroke, dementia which occurs following strokes (post-stroke dementia), post-traumatic craniocerebral trauma, general disturbances of concentration, concentration disturbances in children suffering from learning and memory problems, vascular dementia, dementia associated with Lewy bodies, dementia associated with degeneration of the frontal lobes including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia associated with corticobasal degeneration, amyolateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, new variant Creutzfeld-Jacob dementia, HIV dementia, schizophrenia associated with dementia or Korsakoff's psychosis.

Factors 3 and 7: In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that the prevention or cure of the diseases of claims 1-3

and 7-9, which exhibited some sensitivity to a cGMP-stimulating compound in general, could be effectively achieved by the administration of the claimed active agent. Based on the state of the art, as discussed below, the artisan would have only accepted that the treatment of most of the diseases of claims 1-3 and 7-9 could be achieved, rather than that such an agent could have been used to prevent all known symptoms, with exception to MS and ALS. The artisan would also not have accepted that a cGMP-stimulation compound could effectively treat or prevent MS or ALS.

As set forth in *In re Marzocchi* et al., 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling."

Factor 4: Applicant disclosed guidance in the form of assays for determining the activity of phosphodiesterases, and a method for determining memory performance in rats. Applicant also disclosed how a human might be administered this composition. Still, further guidance is needed in regards to humans. To enable the Artisan to reasonably predict that Applicant's composition can prevent the diseases of claims 1-3

and 7-9, or even treat MS or ALS, Applicant should set forth a protocol or guidance as to how prevention of these diseases could be achieved. Applicant's disclosure is inadequate as to directing or guiding how the proposed agents can be employed to accomplish such objectives in a predictable manner.

Factor 5: While the present claims encompass preventing the diseases of claims 1-3 and 7-9, Applicant's provides no data evidencing a treatment, prevention or cure. No other data has been provided, or reasonable scientific basis exists, for predicting a prevention of the diseases of claims 1-3 and 7-9 or treatment of MS or ALS.

Treatment of dementia, stroke, MS, ALS and coronary artery disease, for example, is well developed (see Dementia: Delirium and Dementia: Merck Manual Professional; see Introduction: Stroke (CVA): Merck Manual Professional; see Multiple Sclerosis (MS): Demyelinating Disorders: Merck Manual Professional; see Motor Neuron Disorders: Peripheral Nervous System Disorders: Merck Manual Professional; see Angina Pectoris: Coronary Artery Disease: Merck Manual Professional; see all at http://merck.com/), but the state of the art with regard to preventing these diseases in general is grossly underdeveloped.

In this regard, The Merck Manuel is cited. In particular, there is no known agent that is effective against preventing dementia, stroke, MS, ALS, or coronary artery disease. The Merck Manuel references clearly show that for dementia, stroke, MS, ALS and coronary artery disease, there is not one agent or combination thereof that is effective at preventing these diseases (see Prognosis and Treatment at pp. 5, 9, 12, and 14 of Dementia; see Treatment at pg. 5 of Stroke; see Prognosis and Treatment at

pg. 4 of Multiple Sclerosis; see Treatment at pg. 4 of Motor Neuron Disorders; see Treatment at pg. 5-7 of Angina Pectoris).

Given that there was not known a specific agent or combination of agents effective to prevent dementia, stroke, MS, ALS or coronary artery disease, one of ordinary skill in the art would not accept on its face Applicant's statement that such an objective could be achieved with any disease of claims 1-3 and 7-9. The artisan would have required sufficient direction as to how to predict what particular diseases would actually show sensitivity to the presently claimed composition such that the artisan would have been imbued with at least a reasonable expectation of success in preventing such diseases. Such success would not have been reasonably expected for preventing symptoms associated with the diseases of claims 1-3 and 7-9 given the variable nature of dementia, stroke, MS, ALS and coronary artery disease. The prevention of the diseases of claims 1-3 and 7-9, for example, would have been an outcome not reasonably expected by one of ordinary skill in the art. To the artisan, the concept of a single agent, or even a combination of agents, that is effective to prevent diseases of claims 1-3 and 7-9 in a mammal would have been unique and, thus, met with a great deal of skepticism.

Furthermore, there is no teaching suggested in Applicant's specification or the references of MS or ALS or that would cause the artisan to reasonably predict that the claimed composition could treat MS or ALS. Further guidance is also needed in regard to treatment of these diseases with a cGMP-stimulating compound.

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the state of the art, which recognizes the variable nature of treating dementia, stroke, MS, ALS and coronary artery disease, there is no apparent disclosure to support the contention that the diseases of claims 1-3 and 7-9 can be prevented by simply administering, by any method, a cGMP-stimulating compound, since the present specification fails to enable one of ordinary skill in the art to practice the entirety of the presently claimed invention.

Factor 6: The burden of preventing diseases of claims 1-3 and 7-9 with the claimed composition is much greater than that of treating diseases of claims 1-3 and 7-9, with specific cGMP-stimulating compounds. Since the present specification would not enable the skilled artisan to prevent diseases of claims 1-3 and 7-9, or treat MS or ALS with the claimed composition, a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice the full scope of the presently claimed invention.

Factor 8: In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

Summary

As the discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue one of ordinary skill with a reasonable expectation that preventing diseases of claims 1-3 and 7-9, or treating MS or ALS with the claimed composition could be achieved. In order to actually achieve

such an objective, it is clear from the discussion above that one of ordinary skill could not rely on Applicant's disclosure as required by 35 U.S.C. § 112, first paragraph. Given that the art fails to recognize, and Applicant as failed to demonstrate, via direct evidence or sound reasoning, that diseases of claims 1-3 and 7-9 can be prevented, or that MS or ALS can be treated with the claimed composition, one of ordinary skill would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Accordingly, claims 1-9 are deemed properly rejected.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 10 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,803,365. Although the conflicting claims are not identical, they are not patentably distinct from each other because the pharmaceutical of claim 10 of the instant application is also an imidazo [1,3,5]triazinone of formula (1) of the '365 patent claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Niewohner et al., (WO 01/47928; 2001), English language equivalent U.S. Patent No. 6,803,365.

Applicant's invention is drawn to a method for treating and or prophylaxis of diseases in which an improvement in and/ or a cure of a syndrome can be achieved by improving the microcirculation of a tissue, which contains a cGMP-metabolizing phosphodiesterase by administering a cGMP-stimulating compound. The diseases can be coronary heart disease, or cardiac insufficiency (claim 2). The method of claim 1 also improves perception, dementia, strokes etc. (claim 3) The cGMP-stimulating compound is an imidazo[1,3,5]triazinone of formula I (claim 4) with further limitations (claim 5, and 6). Applicant also claims a pharmaceutical of at least one cGMP-

stimulating compound (claim 7-9), and an imidazo[1,3,5]triazinine of formula I (claim 10).

Niewohner et al. teach the imidazo[1,3,5]triazinine of formula 1 with the limitations of claims 4, 5 and 6. (See bottom of col. 1 lines 45-67, col. 2 lines 1-67, col. 3 lines 1-20, col. 4 lines 17-67, col. 5 lines 1-67, col. 6 lines 1-67, and col. 7 line 1.) This satisfies the limitations of claims 7-10. Niewohner teach that this compound increases the concentration of cGMP, which can effect short or long-term modulation of vascular and cardiac intropy, as per claim 1. (See col. 1 lines 28-44.) They teach that the compound treats stroke, brain trauma, and dementia (see col. 12 lines 33-38), satisfying the limitations of claims 3 and 9. They also teach that this compound is suitable for the treatment of cardiovascular diseases, as per claim 2. (See col. 12 lines 15-32.)

Note that it is viewed that since Niewohner administers his compound to someone having many different types of "cardiovascular diseases" that it is inevitable that the reference treated coronary heart disease.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niewohner et al., (*supra*).

Niewohner et al. teach the imidazo[1,3,5]triazinine of formula 1 with the limitations of claims 4, 5 and 6. (See bottom of col. 1 lines 45-67, col. 2 lines 1-67, col. 3 lines 1-20, col. 4 lines 17-67, col. 5 lines 1-67, col. 6 lines 1-67, and col. 7 line 1.) This satisfies the limitations of claims 7-10. Niewohner teach that this compound increases the concentration of cGMP, which can effect short or long-term modulation of vascular and cardiac intropy, as per claim 1. (See col. 1 lines 28-44.) They teach that the compound treats stroke, brain trauma, and dementia (see col. 12 lines 33-38). They also teach that this compound is suitable for the treatment of cardiovascular diseases. (See col. 12 lines 15-32.)

Niewohner et al., does not explicitly teach that coronary heart disease is being treated.

It would have been obvious to a person of ordinary skill in the art at the time of applicant's invention to use the compound of Niewohner to treat coronary heart disease since Niewohner teach that the compound can be used to treat many different types of

cardiovascular diseases, which would clearly encompass coronary heart disease, or in the very least it would have been obvious to administer the claimed compound to treat cornary heart disease, since it clearly is a well known type of cardiovascular disease. (See col. 1 lines 35-40; see also col. 12, lines 20-32.)

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 9:00am-5:00pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

WW

JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER